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AUTHOR(S):

Aoyama, Tomoki; Fujita, Yasuko; Madoba, Katsuyuki; Nankaku, Manabu; Yamada, Minoru; Tomita, Motoko; Goto, Koji; ... Matsuda, Shuichi; Nakamura, Takashi; Toguchida, Junya

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ORIGINAL ARTICLE

Rehabilitation Program After Mesenchymal Stromal Cell Transplantation Augmented by Vascularized Bone Grafts for Idiopathic Osteonecrosis of the Femoral Head: A Preliminary Study

Tomoki Aoyama, MD, PhD,[a] Yasuko Fujita, RPT,[b] Katsuyuki Madoba, RPT,[c] Manabu Nankaku, RPT, PhD,[b] Minoru Yamada, RPT, PhD,[a] Motoko Tomita, MD,[c] Koji Goto, MD, PhD,[d] Ryosuke Ikeguchi, MD, PhD,[d] Ryosuke Kakinoki, MD, PhD,[b,d] Shuichi Matsuda, MD, PhD,[b,d] Takashi Nakamura, MD, PhD,[b,d] Junya Toguchida, MD, PhD[e,f]

From the [a]Department of Physical Therapy, Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto; [b]Rehabilitation Unit, Kyoto University Hospital, Kyoto; [c]Department of Rehabilitation, Kyoto Hakuaikai Hospital, Kyoto; [d]Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto; [e]Department of Tissue Regeneration, Institute for Frontier Medical Sciences, Kyoto University, Kyoto; and [f]Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan.
Current affiliation for Nakamura: Department of Orthopaedic Surgery, National Hospital Organization Kyoto Center, Kyoto, Japan.

Abstract

Objective: To determine the feasibility and safety of implementing a 12-week rehabilitation program after mesenchymal stromal cell (MSC) transplantation augmented by vascularized bone grafting for idiopathic osteonecrosis (ION) of the femoral head.

Design: A prospective case series.

Setting: University clinical research laboratory.

Participants: Participants (N = 10) with ION who received MSC transplantation augmented by vascularized bone grafting.

Intervention: A 12-week exercise program, which included range-of-motion (ROM) exercises, muscle-strengthening exercises, and aerobic training.

Main Outcome Measures: Measures of ROM, muscle strength, Timed Up and Go test, and Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) were collected before surgery and again at 6 and 12 months after surgery.

Results: All participants completed the 12-week program. External rotation ROM as well as extensor and abductor muscle strength significantly improved 6 months after treatment compared with that before treatment ($P<.05$). Significant improvements were also seen in physical function, role physical, and bodily pain subgroup scores of the SF-36 ($P<.05$). No serious adverse events occurred.

Conclusions: This study demonstrates the feasibility and safety of a multiplex rehabilitation program after MSC transplantation and provides support for further study on the benefits of rehabilitation programs in regenerative medicine.

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Idiopathic osteonecrosis (ION) of the femoral head is a painful disorder that progresses to femoral head collapse and osteoarthritis of the hip joint.[1,2] This disease mainly affects individuals aged 30 to 40 years.[3] The exact pathologic mechanism of ION remains unknown; however, obstruction of blood flow to the femoral head, which causes death of bone-forming cells, is a hallmark of this condition. Without bone-forming cells, bone tissue gradually loses

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its mechanical properties and eventually collapses, causing articular surface deformities.[1-3]

Recently, surgical treatment has become more common than nonsurgical treatment for ION in the United States.[4] Conservative treatment to offload forces by limiting weight-bearing, activity modification, and physical therapy is thought to have limited success in preventing disease progression.[3,4] If the disease progresses, the patient eventually requires total hip arthroplasty (THA).[1-3] Although the survival rate of THA has improved markedly, individuals with ION are typically young, and THA durability is limited; therefore, joint-preserving treatment is preferred. However, recent data indicate that joint-preserving procedures are performed less often than THA.[3]

Regenerative medicine using cell transplantation is a promising treatment for patients with refractory disease. Mesenchymal stromal cell (MSC) transplantation, for example, is a promising new treatment for joint preservation in ION. MSCs can differentiate into cells of osteogenic, chondrogenic, and adipogenic lineages in vitro.[5-7] During early-stage ION, treatment with MSCs in combination with core decompression surgery has resulted in significant delay and even prevention of femoral head collapse.[8-12] However, in more advanced stages, the result of this procedure has not been satisfactory.[12-14] Because bone marrow pressure is elevated in the early stage of ION,[15] core decompression to reduce the pressure is required. However, in advanced-stage disease, when subchondral bone fractures occur, initial strengthening, instead of decompression, is needed to prevent collapse.[16]

We designed a protocol using a combination of MSCs and vascularized bone grafts for treating advanced stages of ION.[17] Because ION is caused by loss of blood supply and bone-forming cells as well as mechanical vulnerability, vascularized bone grafting is, theoretically, a reasonable treatment for this condition.[16,17] Although MSC transplantation is a promising therapeutic strategy, rehabilitation interventions after surgery may have a significant effect on the ultimate treatment result. However, detailed information about rehabilitation programs after cell transplantation has not yet been reported.[8-14] Moreover, the effect of rehabilitation alone on ION is controversial.[18,19] This study aimed to determine the feasibility and safety of a rehabilitation program that was performed in a clinical trial of MSC transplantation augmented by vascularized bone grafting for ION.

Methods

The current study was a prospective case series of subjects enrolled in a clinical trial. Details of this prospective, open-labeled, proof-of-concept clinical trial, conducted at Kyoto University Hospital, have been previously reported.[17] The study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine and was conducted according to the Declaration of Helsinki. For this clinical trial, participants were recruited via the website page of Kyoto University Hospital and the University Hospital Medical Information Network (UMIN) Clinical Trials Registry.

List of abbreviations:

ION	**idiopathic osteonecrosis**
MSC	**mesenchymal stromal cell**
RM	**repetition maximum**
ROM	**range of motion**
SDIC	**Specific Disease Investigation Committee**
SF-36	**Medical Outcomes Study 36-Item Short-Form Health Survey**
THA	**total hip arthroplasty**

Assessment of necrotic lesion and radiographic stage

Necrotic lesion type and size were assessed using the radiographic classification proposed by the Specific Disease Investigation Committee (SDIC) in Japan (appendix 1).[20] Staging of ION proposed by the SDIC in Japan is a modified version of the system proposed by the Association Research Circulation Osseous Committee.[20]

Inclusion criteria

Patients aged 20 to 50 years with radiographic stage 3A or 3B, according to SDIC staging,[20] were eligible for enrollment. Written informed consent was obtained from all participants in the clinical trial.

Exclusion criteria

Exclusion criteria were a history of transplantation on the affected part of the hip, heavy smoking (Brinkman index >600), current use of warfarin, diabetes mellitus (defined as hemoglobin A1c >9.0%), arteriosclerosis obliterans, pregnancy, malignant disease, myocardial infarction, brain infarction, rheumatoid arthritis, dialysis use, hematologic disease (leukemia, myeloproliferative disorder, myelodysplastic disorder), limited life expectancy, hepatitis B, hepatitis C, human immunodeficiency virus infection, syphilis, hypotension (systolic blood pressure <90mmHg), low body weight (<40kg), loss of marrow function (neutrophil count <1500/mm^3, hemoglobin level <11.0g/dL [men] or <10.0g/dL [women], platelet count <100,000/mm^3), change in medication (bisphosphonates or steroids) within 3 months of the study, and ineligibility determined by a doctor.

MSC transplantation augmented by vascularized bone grafting

Under general anesthesia, 100mL of bone marrow was obtained from the posterior iliac crest. Mononuclear cells containing MSCs were cultured for approximately 2 weeks under 20% partial pressure of oxygen (Po_2) and 5% partial pressure of carbon dioxide (Pco_2) conditions at 37°C.

MSC transplantation was augmented by vascularized bone grafting. Briefly, participants were placed on the table in the supine position. A curved skin incision (modified Smith-Peterson approach) was made from the iliac crest to the anterior aspect of the proximal thigh.[17] The rectus femoris was released, and the anterior aspect of the femoral neck was explored. Then, a cortical window (1.5×4cm) was prepared, through which a bony trough connecting the necrotic area was created under both fluoroscopic and endoscopic guidance. MSCs ($0.5-1.5\times10^8$) premixed with β-tricalcium phosphate granules (Osferion[a]) were transplanted into the cavity created by curettage. Tricortical iliac crest bone was harvested with a vascular pedicle and grafted into the bone trough.[16] Then, the joint capsule and rectus femoris were sutured.

Rehabilitation program

Rehabilitation was performed at a hospital for 12 weeks. During the initial 4 weeks, rehabilitation was performed at an acute care hospital (table 1). Participants continued rehabilitation at a special rehabilitation hospital for 8 additional weeks. During the first 4 weeks,

Table 1 Rehabilitation program

Time Course After Treatment	Side	Day 1	Day 3	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 12	Discharge
Rest level		Bed rest		Wheelchair	Walk on crutch →							Walk on T-cane	
Weight-bearing		NWB →							1/3 WB	1/2 WB	2/3 WB	FWB	
ROM exercise	Transplant				Passive F, E →								
						Passive Ab →							
									Passive R →				
												Active F, E, Ab, R	
	Nontransplant		Passive & active F, E, Ab, R →										
Muscle strength exercise	Transplant								Isotonic (Straight leg raising, no weight) →				
											Isotonic (Straight leg raising, 2-kg weight)		
									Isokinetic F, E →				
										Isokinetic Ad →			
											Isokinetic R →		
												Isokinetic Ab Squat & heel raise	
	Nontransplant		Isometric F, E, Ab, R		→								
												Isokinetic F, E, Ab, R	
									Squat & heel raise →				
				Muscle strength exercise of upper limb →									
Aerobic training											Aerobike →		

Abbreviations: Ab, abduction; Ad, adduction; E, extension; F, flexion; FWB, full weight-bearing; NWB, non—weight-bearing; R, rotation; WB, weight-bearing.

physical therapy was performed for 40 minutes at a time, once a day, 5 days a week. After the initial 4 weeks, it was performed for 60 minutes at a time, twice a day, 6 days a week. The entire rehabilitation program was supervised by skilled physiotherapists, and the specific therapy received was recorded in the participant's medical record.

Participants were kept non−weight-bearing for 6 weeks after transplantation surgery, followed by one-third weight-bearing, one-half weight-bearing, and two-thirds weight-bearing, progressing at 2-week intervals (see table 1). Full weight-bearing was permitted 12 weeks after treatment.

Before performing range-of-motion (ROM) exercises, pain level was assessed using a numeric rating scale. Passive flexion and extension ROM exercises were initiated 2 weeks after treatment on the transplant side. Passive adduction was initiated 3 weeks after treatment, and passive rotation ROM exercise was initiated 6 weeks after treatment. Active ROM exercise in all directions was initiated 12 weeks after treatment (see table 1). Passive and active ROM exercises in all directions were initiated 3 days after treatment on the nontransplant side (see table 1).

For isotonic flexion muscle-strengthening exercise, straight leg raising with no weight was started 6 weeks after treatment on the transplant side (see table 1). Straight leg raising with 2-kg weight was started after 10 weeks. The intensity of exercise was defined by pain level. Each position was held for 5 seconds and performed 5 times. For isokinetic flexion and extension muscle-strengthening exercises, resistance training was started 6 weeks after treatment on the transplant side. The intensity of exercise was increased by increasing the load by 40% to 80% of 10-repetition maximum (RM). Isokinetic adduction exercise was added at 8 weeks, rotation exercise at 10 weeks, and adduction exercise at 12 weeks after treatment. Isokinetic rotation exercise was performed using Coxa Link.[b] Squat and heel raise exercises were performed 12 weeks after treatment. On the nontransplant side, isometric and isokinetic exercises were started 3 days after treatment. If muscle weakness was present, the intensity of exercise was increased by increasing the load by 70% to 100% of 10RM for muscular hypertrophy. If muscle weakness was not present, exercise loading was increased by 60% to 70% of 15RM for muscular endurance. Nontransplant side squat and heel raise exercises were started 6 weeks after treatment. Upper limb muscle-strengthening exercises were performed using Shoulder Link[b] 1 week after treatment (see table 1).

Aerobic training was started 8 weeks after treatment. The intensity of exercise was defined as a target heart rate of 220×(age×0.6) by using an Aerobike Ai[c] for 30 minutes. After discharge, participants continued home exercises and were assessed once a month. Patients were allowed to resume sports and work 6 months after confirmation of bone ossification (see table 1).

Assessment

All participants underwent assessment before treatment and 6 and 12 months after treatment. Passive hip flexion, extension, abduction, and external rotation angles were measured using universal goniometry. Hip flexor, extensor, and abductor strengths were measured using a handheld dynamometer[d] during isometric contraction for 3 seconds with manual resistance. Knee extensor and flexor strengths and lower limb load were assessed using the Iso Force GT-330.[e] Torque was expressed as a percentage of body weight (Nm/kg). Values of lower limb load force were normalized to body weight (N/kg). In the Timed Up and Go test, the time (in seconds) that a participant required to stand from an armless chair (chair seat height, 45cm), walk a distance of 3m, turn, walk back to the chair, and sit down was measured. Health-related quality of life was evaluated using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).[21]

Adverse events

Compliance with the rehabilitation program and adverse events were recorded in each participant's medical record. Adverse events were monitored by the Department of Clinical Trial Design and Management Translational Research Center. Serious adverse events were assessed by the External Data Monitoring Committee.

Statistical analysis

ROM, muscle strength, and SF-36 score were presented as the median with 25% to 75% quartiles. For follow-up assessment of changes in each outcome over time, the Friedman test was used to identify overall significant differences at 3 different time points (before treatment and 6 and 12mo after treatment) for each variable. Post hoc Scheffe test was used to assess which time points showed significant differences. A P value of $<.05$ was considered statistically significant for all analyses.

Results

Between November 2007 and June 2009, 10 participants were recruited into the clinical trial. All participants were men with an average age of 31.7 years (range, 20−48y). A history of steroid treatment was found in 4 participants (table 2). The pretreatment radiographic stage was 3A in 6 hips and stage 3B in 4 hips (see table 2). During the rehabilitation period (6mo after surgery), there was no progression of disease. At 1 year after surgery, 6 hips with stage 3A and 2 hips with stage 3B did not progress, but 2 hips with stage 3B (cases 3 and 7) progressed to stage 4.[17]

Hip ROM

While nearly all ROM measures improved after treatment, the only significant improvements were transplant-side external rotation at 6 months ($P<.05$) and nontransplant-side flexion at 12 months ($P<.01$) (table 3).

Muscle strength and function

While nearly all muscle strength measures improved after treatment, the only significant improvements were transplant-side extensor and abductor strength at 12 months after treatment ($P<.05$) (table 4).

On the nontransplant side, there was significant improvement in lower limb load strength ($P<.05$) (see table 4). The remaining subgroup scores showed posttreatment improvements that did not reach statistical significance.

SF-36 subgroup score

There were significant improvements in physical function, role physical, and bodily pain subgroup scores between the 3 time points (before treatment and 6 and 12mo after treatment) ($P<.05$) (table 5). There was also a significant difference in each score between values before and 12 months after treatment ($P<.05$).

Table 2 Baseline data of patients

Case	Age (y)	Sex	Height (cm)	Weight (kg)	Affected Side	Steroid Use	Class*	Stage†	History
1	27	M	170.9	66.5	R	Y	C2	3B	Nephritis
2	23	M	171.0	56.6	L	Y	C2	3A	Cushing syndrome
3	48	M	174.7	87.5	R	N	C2	3B	Meningioma
4	20	M	174.2	76.8	R	Y	C1	3A	Hepatitis
5	35	M	178.8	70.0	L	N	C2	3A	None
6	28	M	169.2	58.3	R	N	C2	3A	None
7	39	M	183.1	85.2	R	Y	C2	3B	Leukemia
8	26	M	175.1	66.4	R	N	C2	3B	None
9	33	M	174.2	61.0	R	N	C2	3A	None
10	38	M	166.7	52.9	R	N	C2	3A	None

Abbreviations: L, left; M, male; N, no; R, right; Y, yes.
* Radiographic clinical classification proposed by Japanese Investigation Committee.
† Radiographic staging score by Japanese Investigation Committee.

Adverse events

All participants completed the 12-week rehabilitation program. There were 5 cases of muscle pain, 2 cases of muscle stiffness, and 1 case of ankle pain on initiation of load bearing, but no serious adverse events were associated with rehabilitation. Radiography showed no evidence of progression in femoral head collapse during the rehabilitation period.

Discussion

In the current study, we designed a rehabilitation program that focused on 3 aspects: (1) improving hip joint function, (2) avoiding collapse of the femoral head, and (3) promoting bone formation from transplanted cells by using a physical therapy protocol.

In the field of rehabilitation, the relationship between pursuing functional improvement and risk reduction becomes a trade-off in some cases, but compatibility between them is important. To accomplish this trade-off, it is helpful to simultaneously assess the etiologic factors and radiologic findings of these patients in order to treat ION.[22,23] Further, lesion size, lesion location, and radiographic staging can help determine the natural course of ION.[22] In our patients, necrotic lesion size was broad, and radiographic stage had progressed (see table 2). The prognosis for steroid-induced ION is better than that for ION associated with sickle cell anemia.[22] In our study, among the 10 participants, 4 had a history of steroid use, while the other 6 had idiopathic ION (see table 2). The rehabilitation program in patients with ION should consider these aspects and should be planned carefully to avoid collapse of the femoral head.

Weight-bearing was prohibited until 6 weeks after treatment (see table 1), and full-weight sitting-to-standing actions were prohibited until 12 weeks after treatment because of the high pressure placed on the top of the femoral head.[24-26] Not only weight-bearing, but also muscle activity increases the acetabular contact pressure. Isometric hip extension and active hip flexion generate high pressure on the femoral head, equal to weight-bearing and walking.[25,26] By comparison, the pressure generated by isotonic and isokinetic exercises is much less.[25,26] Such joint-

Table 3 Comparison of hip ROM between pretreatment, 6 months after treatment, and 12 months after treatment (N = 10)

Hip ROM	Pretreatment	6mo After Treatment	Effect Size (Pre/6mo)	12mo After Treatment	Effect Size (Pre/12mo)	*P* at 3 Time Points (Pre/6mo/12mo)
Flexion (deg)						
Transplant side	97.5 (95.0—107.5)	107.5 (96.3—110.0)	.58	107.5 (100—113.8)	.74	.19
Nontransplant side	101.0 (100.0—110.0)	112.5 (100.0—113.8)	.31	112.5 (101.3—120.0)*	.47	<.01
Extension (deg)						
Transplant side	20.0 (15.0—20.0)	20 (16.3—20.0)	.12	15.0 (15.0—18.8)	.47	.34
Nontransplant side	20.0 (16.3—20.0)	20.0 (15.0—20.0)	.01	17.5 (15.0—20.0)	0	.92
Abduction (deg)						
Transplant side	30.0 (21.3—35.0)	35.0 (30.0—40.0)	.52	35.0 (30.0—38.8)	.38	.24
Nontransplant side	35.0 (31.3—38.8)	37.5 (31.3—40.0)	.23	35.0 (35.0—35.0)	.11	.53
External rotation (deg)						
Transplant side	45.0 (37.5—53.8)	50.0 (41.3—60.0)†	.43	50.0 (42.5—53.8)	.31	.09
Nontransplant side	40.0 (37.5—53.8)	50.0 (45.0—60.0)	.46	50.0 (45.0—60.0)	.42	.38

NOTE. Values are median (25%—75% quartiles) or as otherwise indicated. *P* values at 3 time points were calculated by Friedman test. Multiple comparison test was performed by Scheffe test.
* $P<.01$.
† $P<.05$ as calculated by comparison with pretreatment.

Table 4 Comparison of physical function between pretreatment, 6 months after treatment, and 12 months after treatment (N=10)

Measure	Pretreatment	6mo After Treatment	Effect Size (Pre/6mo)	12mo After Treatment	Effect Size (Pre/12mo)	*P* at 3 Time Points (Pre/6mo/12mo)
Hip flexor strength (Nm/kg)						
Transplant side	1.39 (1.01–1.65)	1.49 (1.35–1.86)	0.74	1.79 (1.58–1.91)	0.70	.12
Nontransplant side	1.30 (1.05–1.50)	1.82 (1.38–1.96)	1.14	1.73 (1.68–2.03)	1.12	.08
Hip extensor strength (Nm/kg)						
Transplant side	0.56 (0.43–0.78)	1.48 (0.84–1.56)	0.98	1.28 (0.86–1.69)*	1.00	<.05
Nontransplant side	0.64 (0.37–0.80)	1.13 (0.82–1.49)	1.18	1.61 (0.96–1.77)	1.62	.08
Hip abductor strength (Nm/kg)						
Transplant side	0.67 (0.51–1.29)	1.20 (0.81–1.43)	0.58	1.28 (1.05–1.78)*	0.86	<.05
Nontransplant side	0.66 (0.52–1.37)	1.21 (0.88–1.66)	0.53	1.28 (1.21–1.85)	0.71	.20
Knee flexor strength (Nm/kg)						
Transplant side	1.36 (1.18–1.79)	1.55 (1.32–1.81)	0.38	1.63 (1.37–1.71)	0.47	.15
Nontransplant side	1.36 (1.11–1.70)	1.50 (1.12–1.66)	0.29	1.55 (1.27–1.58)	0.37	.07
Knee extensor strength (Nm/kg)						
Transplant side	2.77 (2.24–3.37)	2.97 (2.42–4.09)	0.46	3.22 (2.93–3.69)	0.56	.10
Nontransplant side	2.71 (2.50–4.00)	3.38 (2.98–3.83)	0.49	3.51 (2.72–4.10)	0.36	.19
Lower limb load (N/kg)						
Transplant side	10.61 (8.01–14.58)	15.78 (9.16–20.02)	0.99	15.34 (12.04–19.74)	0.98	.06
Nontransplant side	14.16 (10.36–20.65)	17.61 (12.49–21.72)	0.47	18.04 (14.12–23.50)*	0.70	<.05
Timed Up and Go test (s)	7.06(5.82–7.31)	6.11 (4.96–7.00)	0.51	5.40 (5.00–6.50)	0.77	.15

NOTE. Values are median (25%–75% quartiles) or as otherwise indicated. *P* values at 3 time points were calculated by Friedman test. Multiple comparison test was performed by Scheffe test.
* *P*<.05, as calculated by comparison with pretreatment.

preserving, muscle-strengthening exercise has been reported in physical therapy for osteoarthritis.[27,28] We designed the rehabilitation program so that isotonic and isokinetic exercises could be performed on the transplant side before isometric exercises (see table 1). All participants completed the 12-week rehabilitation program without excessive pain. Functional improvement was observed, and there were no serious adverse events associated with rehabilitation. These results suggest that the first 2 aims of our study were achieved.

Although we could not show clear evidence that the current rehabilitation program promotes bone formation, mechanical stimulation may be important for bone formation of transplanted cells. Lack of mechanical loading causes bone loss and fractures in the elderly.[29] During physical activity, mechanical forces are placed on the bones through ground reaction forces and the contractile activity of muscles.[30,31] Adapting physical forces to bone structure results in maintenance and prevention of fractures in the elderly.[30] Fluid flow, strain, and hydrostatic pressure are mechanotransducers of physical force to osteocytes.[29,31,32] Stimulated mechanoreceptors on osteocytes activate the prostaglandin and Wnt pathways.[33] Mechanical loading stimulates not only osteocytes but also osteoblasts[34,35] and MSCs.[36,37] Oscillatory fluid flow promotes the proliferation and differentiation of marrow MSCs.[37] Furthermore,

Table 5 Comparison of SF-36 subgroups scores between pretreatment, 6 months after treatment, and 12 months after treatment (N=6)

SF-36 Subgroups	Pretreatment	6mo After Treatment	Effect Size (Pre/6mo)	12mo After Treatment	Effect Size (Pre/12mo	*P* at 3 Time Points (Pre/6mo/12mo)
Physical function	45 (36.3–65)	90 (78.8–95)	1.54	92.5 (78.8–95)*	1.58	<.05
Role-physical	40.6 (36.3–78.1)	68.8 (57.8–93.8)	0.71	96.9 (93.8–100)*	1.63	<.05
Bodily pain	52 (51.3–52)	72 (64.5–72)	2.83	73 (64.5–81.5)*	3.18	<.05
General health	59.5 (49.5–77)	77 (61.8–90.8)	0.66	79.5 (62–88)	0.72	.31
Vitality	71.9 (54.7–84.4)	68.8 (62.5–84.4)	0.22	71.9 (62.5–85.9)	0.11	.58
Social function	31.3 (25–84.4)	100 (71.9–100)	0.90	93.8 (78.2–100)	1.00	.21
Role-emotion	50 (37.5–87.5)	100 (100–100)	0.89	100 (100–100)	1.15	.13
Mental health	80 (71.2–88.8)	90 (82.5–90)	0.52	80 (80–83.4)	0.44	.27

NOTE. Values are median (25%–75% quartiles) or as otherwise indicated. *P* values at 3 time points were calculated by Friedman test. Multiple comparison test was performed by Scheffe test.
* *P*<.05 as calculated by comparison with pretreatment.

mechanical signals inhibit adipogenesis and promote the anabolism of osteogenesis.[36] A report by Ambrosio et al[38] reveals important information about this issue. Treadmill running has a synergistic effect on healing injured skeletal muscle after muscle-derived stem cell transplantation,[38] in addition to the positive effects of improved weight management, cardiovascular health, and metabolic profile.[39] Our previous report[40] suggested that adequate exercise promotes muscle remodeling after bilateral broad necrosis of the soleus muscles. It is hypothesized that suitable mechanical stimulation drives the differentiation of MSCs, while the beneficial paracrine effect may induce a synergistic effect between MSC transplantation and rehabilitation. However, further basic and clinical research is required to prove this hypothesis.

Evaluation of the effect of nonsurgical procedures on ION is important. Mont et al[18] compared the effect of core decompression surgery with nonsurgical management of ION and reported a 63.5% satisfactory clinical result with core decompression, but only 22.7% with nonsurgical management. However, this study was not an adjusted case-control study but was a literature review. Therefore, etiologic factors and radiographic findings were not fully assessed.[18] In multicenter, randomized controlled studies, physical therapy has similar effects in ION patients with sickle cell disease as does core decompression surgery with physical therapy.[19,41] Basic studies to design the rehabilitation protocol and further clinical studies are needed, but the information provided from the current study may aid in the development of rehabilitation protocols after cell transplantation for the treatment of ION.

Study limitations

The current study has several major limitations. This was a small-scale, single-group, pre-post preliminary study. Case-control and large-scale studies are needed to demonstrate the efficacy of the rehabilitation protocol. The current study was based on the original clinical trial, so it is not an individual study. The population size of the clinical trial itself was limited because it was a feasibility study.

Conclusions

The present study demonstrated the feasibility and safety of an intensive multiplex rehabilitation program after MSC transplantation in individuals with ION. Despite this, future studies should investigate dosing and timing parameters, as well as the mechanistic basis for improvements in outcomes when a combination therapy is used.

Suppliers

a. Olympus Terumo Biomaterials Co.
b. Senoh Co.
c. KONAMI Co.
d. Nihon Medix Co Ltd.
e. OG Giken Co Ltd.

Keywords

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Corresponding author

Tomoki Aoyama, MD, PhD, Department of Physical Therapy, Human Health Sciences, Graduate School of Medicine, Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. *E-mail address:* blue@hs.med.kyoto-u.ac.jp.

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Appendix 1 Assessment of Necrotic Lesions and Stages

Radiographic classification proposed by the SDIC in Japan[20]:

- Type A lesions occupied the medial one third or less of the weight-bearing portion.
- Type B lesions occupied the medial two thirds or less of the weight-bearing portion.
- Both types C1 and C2 lesions occupied more than the medial two thirds of the weight-bearing portion.
- Type C2 lesions extended laterally to the acetabular edge, but type C1 lesions did not.

The ION staging proposed by the SDIC used in Japan is a modified version of the system proposed by the Association Research Circulation Osseous Committee.[20]

- *Stage 1:* Specific findings of osteonecrosis are not observed on magnetic resonance imaging, bone scintigram, histology, or radiographs.
- *Stage 2:* Demarcating sclerosis is seen without collapse of the femoral head.
- *Stage 3:* Collapse of the femoral head, including the crescent sign, is seen without joint-space narrowing. Mild osteophyte formation of the femoral head or acetabulum may be seen.
  - *Stage 3A:* Collapse of the femoral head $<$3mm
  - *Stage 3B:* Collapse of the femoral head $\geq$3mm
- *Stage 4:* Osteoarthritic changes are seen.

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